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Title

Process for preparing N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine

Patent Assignee

SOUTH CHINA UNIV OF SCIENCE AN

Inventor(s)

WU FANHONG; TANG GUOZHENG

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Abstract

(CN1364757)

The present invention is the preparation of N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3- phenylpropylamine as an important medicinal intermediate for preparing efficient urinary incontinence treating medicine Toterodine and other medicine. The present invention prepares N,N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3- phenylpropylamine by using 6-methyl-4-phenyl-3,4-coumaran as raw material and through four reaction steps of ring opening methylation, amidation, reduction and demethylating. The present invention has short technological path, high yield, cheap material, mild reaction condition and low cost, and may be used in industrial production.

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TANG GUOZHENG

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代理人 文琦

权利要求书 2 页 说明书 5 页 附图页数 0 页

[54] 发明名称 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备方法

[57] 摘要

本发明公开了一种 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备方法。N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺是一种重要的医药中间体,也是制备 高效抗尿失禁新药托特罗定的重要中间体,本发明以 6-甲基-4-苯-3,4-二氢香豆素 为原料,经过开环甲基化,酰胺化,还原,脱甲基化四步反应制得 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺。本发明的方法反应缩短了工艺路线,提高了收率;采用廉价易得的原料、试剂,实现了多位阻低活性酰胺的还原,大大降低了生产成本;反应条件温和,可实现工业化生产。

权 利 要 求 书

1. 一种 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备方法, 其特征在于, 该方法包括如下步骤:

(1) 以 6-甲基-4-苯-3,4-二氢香豆素为原料, 以碱性物质为催化剂与硫酸二甲酯反应, 然后从反应产物中采用常规的方法收集化合物 3-(2-甲氧基-5-甲基苯基)-3-苯丙酸;

反应时间为 2-5 小时, 反应温度为 10-90℃;

(2) 以上述反应产物为原料, 苯或二氯甲烷为溶剂, 在吡啶催化下, 与酰化试剂在 50-100℃下反应 1-5 小时, 再在 -10~-25℃ 下与二异丙胺在 15-35℃下反应 1-4 小时, 然后从反应产物中收集 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺;

(3) 以步骤 2 的反应产物为原料, 先与络合试剂生成离子衍生物, 再与还原试剂反应, 还原得到 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺;

反应时间为 2-10 小时, 反应温度为 10-100℃;

(4) 以步骤 3 的反应产物为原料, 与吡啶和卤化氢溶液或吡啶噻唑化物反应, 然后从产物中用常规的方法收集目标产物 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺;

反应时间 1-5 小时, 反应温度 100-250℃。

2. 如权利要求 1 所述的方法, 其特征在于, 步骤 (1) 中各物料的摩尔比为: 6-甲基-4-苯-3,4-二氢香豆素: 碱性物质: 硫酸二甲酯=1: 1~5: 1.2~5;

所说的碱性物质为碱金属氢氧化物或碱金属碳酸盐及其混合物。

3. 如权利要求 1 所述的方法, 其特征在于, 步骤 (2) 中各物料的摩尔比为: 3-(2-甲氧基-5-甲基苯基)-3-苯丙酸: 酰化试剂: 二异丙胺=1: 2~15: 1~8;

所说的酰化试剂包括 POCl_3 、 SOCl_2 、 PCl_5 或 PCl_3 中的一种。

4. 如权利要求 1 所述的方法, 其特征在于, 步骤 (3) 中各物料的摩尔比为: N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺: 络合试剂: 还原试剂=1: 1.2~20: 2~8;

所说的络合试剂为 POCl_3 、 SOCl_2 、 PCl_5 、 AlCl_3 、 TiCl_4 、 FeCl_3 中的一种；

所说的还原试剂包括锌粉、硼氢化钠、硼氢化钾或铁粉。

5. 如权利要求 1 所述的方法，其特征在于，以步骤（3）的反应产物为原料，与 2-8 倍摩尔比的吡啶和 3-10 倍摩尔比的卤化氢或吡啶噻卤化物反应。

6. 如权利要求 1 或 2 所述的方法，其特征在于，步骤（1）的 $\text{pH}=8\sim 12$ 。

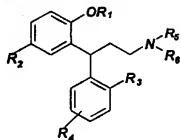
N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备方法

技术领域

本发明涉及 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备方法。

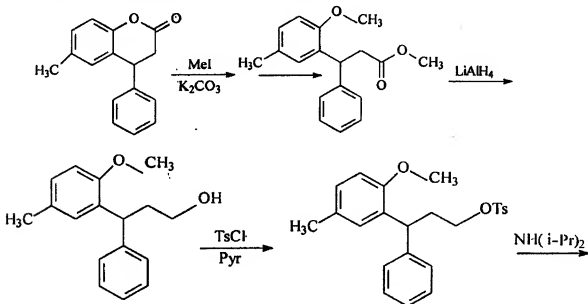
技术背景

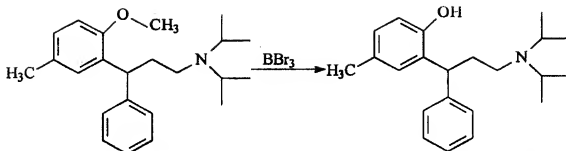
N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺是一种重要的医药中间体，也是制备高效抗尿失禁新药托特罗定的重要中间体，其结构通式如下：



其中， $R_2 = \text{Me}$ ， $R_1, R_3, R_4 = \text{H}$ ， $R_5, R_6 = \text{CH}(\text{CH}_3)_2$ 。

欧洲专利 (EP 0325571) 曾对托特罗定进行了报道，其中即涉及 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备方法。





上述专利所披露的技术以 6-甲基-4-苯-3, 4-二氢香豆素为原料, 经过五步反应制备得 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺, 该方法存在着十分明显的缺陷:

- 1) 采用碘甲烷使香豆素开环, 碘甲烷价格昂贵, 成本太高。
- 2) 采用 LiAlH_4 对酯还原。 LiAlH_4 很活泼, 易燃易爆, 需无水操作, 操作要苛刻; 且 LiAlH_4 价格十分昂贵, 成本太高, 故不能实现工业化生产及利润要求。
- 3) 采用 BBr_3 实现脱甲基反应, BBr_3 价格较昂贵, 成本太高。

发明内容

本发明需要解决的技术问题是公开一种 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺新的制备方法, 以克服现有技术存在的缺陷。

本发明以 6-甲基-4-苯-3, 4-二氢香豆素为原料, 经过开环甲基化, 酰胺化, 还原, 脱甲基化四步反应制得 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺。

本发明的方法包括如下步骤:

(1) 3-(2-甲氧基-5-甲基苯基)-3-苯丙酸的合成: 以 6-甲基-4-苯-3, 4-二氢香豆素为原料, 以碱性物质为催化剂与硫酸二甲酯反应, 然后从反应产物中采用常规的方法收集化合物 3-(2-甲氧基-5-甲基苯基)-3-苯丙酸;

反应时间为 2-5 小时, 反应温度为 $10-90^\circ\text{C}$., $\text{pH}=8-12$, 各物料的摩尔比为:

6-甲基-4-苯-3, 4-二氢香豆素: 碱性物质: 硫酸二甲酯 = 1: 1~5: 1.2~5;

所说的碱性物质为碱金属氢氧化物或碱金属碳酸盐及其混合物, 如氢氧化钠、氢氧化钾、碳酸钠或碳酸钾等中的一种及其混合物;

其中: 6-甲基-4-苯-3, 4-二氢香豆素, 由肉桂酸和对甲基苯酚在浓硫酸催化下合成, 具体合成方法可参见文献《Simpson and Israelstam, *J.S.African Chem. Inst.*, 1949, 2, 165.》所报道的技术;

(2) N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺的合成: 以 3-(2-甲氧基-5-甲基苯基)-3-苯丙酸为原料, 苯或二氯甲烷为溶剂, 在吡啶催化下, 与酰化

试剂在 50-100℃下反应 1-5 小时,再在-10-25℃ 下与二异丙胺在 15-35℃下反应 1-4 小时,冷却,酸洗至 pH=2-5,分离,有机相干燥,石油醚重结晶,得到 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺;各物料的摩尔比为:

3-(2-甲氧基-5-甲基苯基)-3-苯丙酸:酰化试剂:二异丙胺=1:2~15:1~8;

所说的酰化试剂包括 POCl_3 、 SOCl_2 、 PCl_5 或 PCl_3 等中的一种;

(3) 化合物 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺的合成:以 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺为原料,先与络合试剂生成离子络合物,再与还原试剂反应,还原得到 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺。其中酰胺可回收。

反应时间为 2-10 小时,反应温度为 10-100℃;各物料的摩尔比为:

N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺:络合试剂:还原试剂
=1:1.2~20:2~8;

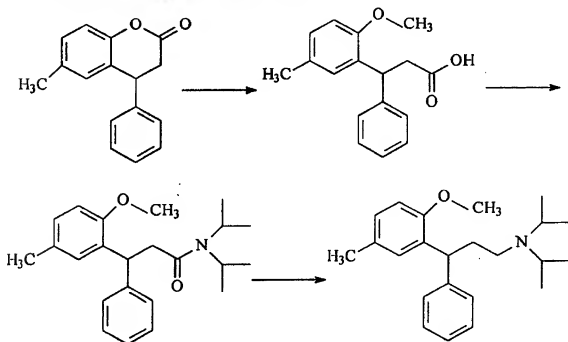
所说的络合试剂为 POCl_3 、 SOCl_2 、 PCl_5 、 AlCl_3 、 TiCl_4 、 FeCl_3 等中的一种;

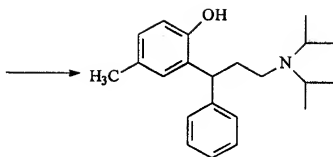
所说的还原试剂包括锌粉或硼氢化钠等中的一种;

(4) 化合物 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的合成:以 N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺为原料,与 2-8 倍摩尔比的吡啶和 3-10 倍摩尔比的卤化氢溶液或吡啶喹啉化物反应,然后从产物中用常规的方法收集目标产物 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺;

反应时间 1-5 小时,反应温度 100-250℃。

上述四个反应步骤的反应式如下所示:





由上述公开的技术方案可见，本发明的方法反应缩短了工艺路线，提高了收率；采用廉价易得的原料、试剂，实现了多位阻低活性酰胺的还原，大大降低了生产成本；反应条件温和，可实现工业化生产。

具体实施方式

实施例 1

化合物 3- (2-甲氧基-5-甲基苯基) -3-苯丙酸的制备：

取 4.76 克 (0.02mol) 6-甲基-4-苯-3, 4-二氢香豆素置于 50ml 三口烧瓶中，加入 10ml 22% 的氢氧化钠水溶液，在 20℃ 下滴加 5.02 克 (0.042mol) 硫酸二甲酯，反应温度在 20℃，搅拌 1 小时。再加入 6ml 17% 的氢氧化钠水溶液，搅拌回流反应 2 小时至澄清，冷却至 30℃，加入过量浓盐酸 (8ml, pH=2)，油层缓慢结晶，过滤，水洗，干燥。用 16 ml 异丙醇重结晶，即得到 3- (2-甲氧基-5-甲基苯基) -3-苯丙酸 5.1g，收率 91%。

mp 133-134℃.

¹H-NMR(ppm, CDCl₃):

2.18(s, 3H), 3.10(d, 2H), 3.73(s, 3H), 4.90(t, 1H), 7.20(m, 8H)

实施例 2

化合物 N, N-二异丙基-3- (2-甲氧基-5-甲基苯基) -3-苯丙酰胺的制备：

取 10 克 (37mmol) 3- (2-甲氧基-5-甲基苯基) -3-苯丙酸溶于 40ml 苯中，加入 5 滴吡啶，再滴加 30ml 二氯亚砷，加热，60℃ 反应 4 小时。减压蒸除二氯亚砷和苯。残留物溶于 40ml 苯，在 0℃ 滴加 25ml (179mmol) 二异丙胺，25℃ 反应 2 小时，倒入 150ml 冰水中，加入 45ml 10% 的盐酸，pH=3，分离有机相，无水硫酸钠干燥。蒸除溶剂，残留物用 20ml 石油醚重结晶，得到 N, N-二异丙基-3- (2-甲氧基-5-甲基苯基) -3-苯丙酰胺 9.3g，收率 71%。

mp 82-83℃.

¹H-NMR(ppm,CDCl₃):

1.20(m,12H),2.22(s,3H),3.30(d,2H),3.38(m,1H),3.70(s,3H),4.05(m,1H),
4.90(t,1H),7.20(m,8H) .

实施例 3

化合物 N, N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺的制备:

取 3.53g (0.01 mol) N, N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙酰胺置于 100 ml 三口烧瓶, 加入 30 ml 三氯氧磷, 加热至 80℃. 反应 3 小时. 20℃ (10mm) 减压蒸干过量的三氯氧磷. 称取 5.0 克活化锌粉, 加入 40ml 无水乙醇, 配成悬浊液, 在冰盐浴冷却 (5℃) 下, 缓慢加入上述反应体系, 加热, 78℃ 回流 2 小时. 蒸除乙醇, 分别用 10ml 乙酸乙酯, 10ml 水, 10ml 乙酸乙酯洗, 抽滤. 将滤液混合, 加入 2% 的乙酸水溶液 60ml, 调节 pH=3, 搅拌 3 小时. 分液, 酯相回收, 得到 1.8g 酰胺. 往水相中加入 20ml 乙酸乙酯, 用 35ml 氨水碱化, pH=10, 搅拌 3 小时. 分液, 酯相干燥, 过滤, 旋干, 得 1.4gN, N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺. 收率 86%.

¹H-NMR(ppm,CDCl₃):

0.95(m,12H), 2.15(m,2H), 2.30(s,3H), 2.38(m,2H),
3.02(t,2H), 3.72(s,3H), 4.38(t,1H), 7.20(m,8H)

实施例 4

化合物 N, N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺的制备:

取 5.0 克 (14.75mmol) N,N-二异丙基-3-(2-甲氧基-5-甲基苯基)-3-苯丙胺, 搅拌下加入 3.6ml(45mmol)吡啶, 5ml 浓盐酸, 反应 0.5 小时. 减压 (0.1Mpa) 蒸馏, 残留物加热至 210℃, 反应 2 小时. 冷却至 25℃, 加入 1ml 水, 加热 80℃ 反应 15 分钟, 冷却至 25℃. 加入 4ml 2N 的盐酸, 抽滤, 干燥. 用 10ml 无水乙醇重结晶, 得到 N,N-二异丙基-3-(2-羟基-5-甲基苯基)-3-苯丙胺盐酸盐 3.6 克, 收率 75%, mp209-211℃.

¹H-NMR(ppm,CDCl₃):

1.20(m,12H), 2.15(s,3H), 2.70(m,2H), 2.90(m,2H),
3.51(t,2H), 4.50(t,1H), 7.25(m,8H) .

NAME OF INVENTION: A method for the preparation of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine

ABSTRACT: The present invention involves a method for the preparation of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, a key intermediate for the synthesis of tolterodine, a new bladder-selective antimuscarinic agent. In the present invention, N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine is prepared from 6-methyl-4-phenyl-3,4-coumaran via four reaction steps including ring opening methylation, amidation, reduction and demethylation. The present invention has the advantages of short preparation process, high yield, cheap materials and reagents, mild reaction conditions, low cost, and is therefore suitable for industrial-scale production.

Claims

What is claimed is:

1. A method for the preparation of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine characterized in that it comprises the following steps:
 - (1) Raw material 6-methyl-4-phenyl-3,4-coumaran is reacted with dimethyl sulfate using an alkaline substance as catalyst, and the product 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid is collected using a common technique;
Duration of the reaction is from 2 to 5h with the temperature ranging from 10°C to 90°C;
 - (2) The above product is reacted with an amidation reagent using benzene or dichloromethane as solvent in the presence of pyridine catalyst at 50~100°C for 1~5h, following which, at -10~-25°C, diisopropylamine is added and reaction is carried out at 15~35°C for 1~4h, the product N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide is collected using a common technique;
 - (3) The product of step (2) and a complexing reagent are reacted to form an ionic derivative, which is reacted with a reducing reagent to give N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine;
Duration of the reaction is from 2 to 10h with the temperature ranging from 10°C to 100°C;
 - (4) The product of step (3) is reacted with pyridine and hydrogen halide solution or pyridinium halide, the target compound N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine is collected using a common technique;
Duration of the reaction is from 1 to 5h with the temperature ranging from 100°C to 250°C.
2. The preparation method according to claim 1 is characterized in that in step (1) the mole ratio of 6-methyl-4-phenyl-3,4-coumaran to alkaline substance to dimethyl sulfate is 1:1~5:1.2~5;
The said alkaline substance is alkali metal hydroxides, alkali metal carbonates or their mixtures.
3. The preparation method according to claim 1 is characterized in that in step (2) the mole ratio of 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid to amidation reagent to diisopropylamine is 1:2~15:1~8;
The said amidation reagent may be one of POCl₃, SOCl₂, PCl₅ or PCl₃.
4. The preparation method according to claim 1 is characterized in that in step (3) the mole

ratio of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide to complexing reagent to reducing reagent is 1:1.2~20:2~8.

The said complexing reagent is one of POCl_3 , SOCl_2 , PCl_5 , AlCl_3 , TiCl_4 or FeCl_3 ; the said reducing reagent is one of zinc powder, sodium borohydride, potassium borohydride or iron powder.

5. The preparation method according to claim 1 is characterized in that the product obtained in step (3) is reacted with a 2- to 8-fold molar excess of pyridine and a 3- to 10-fold excess of hydrogen halide solution or pyridinium halide.
6. The preparation method according to claims 1 and 2 is characterized in that the pH in step (1) ranges from 8 to 12.

Description

A method for the preparation of N, N-diisopropyl-3-(2-hydroxy
-5-methylphenyl)-3-phenylpropylamine

TECHNICAL FIELD

The present invention involves the preparation of N, N-diisopropyl-3-(2-hydroxy
-5-methylphenyl)-3-phenylpropylamine.

BACKGROUND OF THE INVENTION

N, N-diisopropyl-3-(2-hydroxy -5-methylphenyl)-3-phenylpropylamine is an important
pharmaceutical intermediate, it is also a key intermediate for the synthesis of tolterodine, a
new bladder-selective antimuscarinic agent. It has the following structural formula:

[Insert Diagram]

wherein, $R_2=Me$, R_1 , R_3 and $R_4=H$, R_5 , $R_6=CH(CH_3)_2$.

Tolterodine was discussed in a published *European patent application EP0325571*
wherein the preparation of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-
phenylpropylamine was involved.

[Insert Diagram]

[Insert Diagram]

It was disclosed in the above patent that N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine was prepared from 6-methyl-4-phenyl-3,4-coumaran via five reaction steps, and this method had several obvious disadvantages:

- 1) The ring opening process of coumaran is carried out with iodomethane, since it is an expensive reagent, the cost is high.
- 2) Reduction of ester is carried out with LiAlH_4 , since LiAlH_4 reacts violently with water and is known to be highly inflammable and explosive, the process has to be carried out under strictly anhydrous conditions, requirement is hence harsh; furthermore, since LiAlH_4 is an expensive reagent, the cost is high, it is therefore not feasible for industrial-scale production.
- 3) Demethylation is carried out with BBr_3 , and since it is an expensive reagent, the cost is high.

CONTENT OF INVENTION

The purpose of the present invention is to provide a new preparation method of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine to overcome the disadvantages of existing methods.

In the present invention, N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine is prepared from 6-methyl-4-phenyl-3,4-coumaran via four reaction steps including ring opening methylation, amidation, reduction and demethylation.

The method in the present invention comprises the following steps:

- 1) Synthesis of 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid: Raw material 6-methyl-4-phenyl-3,4-coumaran is reacted with dimethyl sulfate using an alkaline substance as catalyst, and the product 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid is collected using a common technique;
Duration of the reaction is from 2 to 5h with the temperature ranging from 10°C to 90°C , pH is 8~12, and the mole ratio of 6-methyl-4-phenyl-3,4-coumaran to alkaline substance to dimethyl sulfate is 1:1~5:1.2~5;

The said alkaline substance is alkali metal hydroxides, alkali metal carbonates or

their mixtures, which may be selected from sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate etc., and mixtures thereof;

wherein: 6-methyl-4-phenyl-3,4-coumaran is prepared through the reaction of cinnamic acid and 4-methylphenol in the presence of catalyst concentrated sulfuric acid (refer to published article {Simpson and Israelstam, J. S. African Chem. Inst., 1949, 2, 165.} for details);

- 2) Synthesis of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide: 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid is reacted with an amidation reagent using benzene or dichloromethane as solvent in the presence of pyridine catalyst at 50~100°C for 1~5h, following which, at -10~-25°C, diisopropylamine is added and reaction is carried out at 15~35°C for 1~4h, after cooling, the reaction solution is washed with acid till pH is 2~5 to allow layers to separate, the organic phase is then dried and recrystallized from petroleum ether to give N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide; the mole ratio of 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid to amidation reagent to diisopropylamine is 1:2~15:1~8;

the said amidation reagent is one of POCl₃, SOCl₂, PCl₅ or PCl₃;

- 3) Synthesis of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine: N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide and a complexing reagent are reacted to form an ionic derivative, which is reacted with a reducing reagent to give N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine. The amide is recoverable.

Duration of the reaction is from 2 to 10h in the temperature range from 10°C to 100°C; the mole ratio of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide to complexing reagent to reducing reagent is 1:1.2~20:2~8; the said complexing reagent is one of POCl₃, SOCl₂, PCl₅, AlCl₃, TiCl₄ or FeCl₃; the said reducing reagent is one of zinc powder or sodium borohydride;

- 4) Synthesis of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine: N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine is reacted with a 2- to 8-fold molar excess of pyridine and a 3- to 10-fold excess of hydrogen halide solution or pyridinium halide, the target compound N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine is collected using a common technique;

Duration of the reaction is from 1 to 5h with the temperature ranging from 100°C to 250°C.

Reaction formulas of the above four reaction steps are shown as follows:

[Insert Diagram]

It is evident from the above technical plan that the present invention has several advantages including short preparation process, high yield, cheap materials and reagents, mild reaction conditions, low cost, and is therefore suitable for industrial-scale production.

PRACTICAL EXAMPLES

Example 1

Preparation of 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid

4.76g (0.02mol) of 6-methyl-4-phenyl-3,4-coumaran was placed in a 50ml three-necked flask, then 10ml of 22% aqueous sodium hydroxide solution was added, followed by 5.02g (0.042mol) of dimethyl sulfate (added drop wise at 20°C), and the mixture was reacted at 20°C for 1h with stirring. Thereafter, 6ml of 17% aqueous sodium hydroxide solution was added and the mixture was reacted under reflux with stirring for another 2h till it became translucent. After cooling to 30°C, an excess of concentrated hydrochloric acid (8ml, pH=2) was added to allow the oil layer to crystallize gradually, followed by filtering, washing with water, drying and recrystallization from isopropanol (16ml) to give 5.1g of 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid, yield was 91%, mp133~134°C, ¹H-NMR (ppm, CDCl₃): 2.18 (s, 3H), 3.10 (d, 2H), 3.73 (s, 3H), 4.90 (t, 1H), 7.20 (m, 8H).

Example 2

Preparation of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide

10g (37mmol) of 3-(2-methoxy-5-methylphenyl)-3-phenylpropionic acid was placed in 40ml of benzene, then 5 drops of pyridine were added, followed by 30ml of thionyl chloride added drop wise, the mixture was then heated and reacted at 60°C for 4h. Thereafter, the thionyl chloride and benzene were removed by evaporation under reduced pressure and the residue was dissolved in 40ml of benzene before 25ml (179mmol) of diisopropylamine was added drop wise at 0°C, and the mixture was reacted at 25°C for 2h. The reaction solution was poured into 150ml of ice water, then 45ml of 10% hydrochloric acid was added to bring the pH to 3. The organic phase was separated and dried over anhydrous sodium sulfate. After the solvent was removed by evaporation, the residue was subjected to recrystallization from petroleum ether (20ml) to give 9.3g of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide, yield was 71%, mp82~83°C. ¹H-NMR (ppm, CDCl₃): 1.20 (m, 12H), 2.22 (s, 3H), 3.30 (d, 2H), 3.38 (m, 1H), 3.70 (s, 3H), 4.05 (m, 1H), 4.90 (t, 1H), 7.20(m, 8H).

Example 3

Preparation of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine

3.53g (0.01mol) of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropanamide was placed in a 100ml three-necked flask, then 30ml of phosphorus oxychloride was added, and the mixture was heated to 80°C and reacted for 3h. Thereafter, excess phosphorus oxychloride was vaporized to dry under reduced pressure at 20°C (10mm). In the meantime, a suspension of activated zinc powder (5.0g) dispersed in 40ml of anhydrous ethanol was prepared, and whilst cooling over an ice-salt bath (5°C), the suspension was added gradually to the above reaction system. Following which, the mixture was heated and refluxed at 78°C for 2h. After the ethanol was removed by evaporation, the resulting residue was washed with 10ml of ethyl acetate, 10ml of water and 10ml of ethyl acetate, respectively, followed by filtration under suction. The filtrates were combined, then 60ml of 2% aqueous acetic acid solution was added to bring pH to 3 and stirred for 3h. The layers were separated, then 1.8g of amide was recovered from the ester layer. To the aqueous layer was added 20ml of ethyl acetate, which was alkalinized with 30ml of aqueous ammonia to bring pH to 10 and stirred for 3h. The layers were separated, the ester phase was dried, filtered and dried in vacuo to give 1.4g of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine, yield was 86%. ¹H-NMR (ppm, CDCl₃): 0.95 (m, 12H), 2.15 (m, 2H), 2.30 (s, 3H), 2.38 (m, 2H), 3.02 (t, 2H), 3.72 (s, 3H), 4.38 (t, 1H), 7.20 (m, 8H).

Example 4

Preparation of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine

5.0g (14.75mmol) of N, N-diisopropyl-3-(2-methoxy-5-methylphenyl)-3-phenylpropylamine was obtained, then 3.6ml (45mmol) of pyridine and 5ml of concentrated hydrochloric acid were added with stirring, and the mixture was reacted for 0.5h, followed by distillation under reduced pressure (0.1MPa). The resulting residue was heated to 210°C and reacted for 2h. After cooling to 25°C, to the reactant was added 1ml of water and the mixture was heated to 80°C and reacted for another 15 minutes, then cooled to 25°C, thereafter, 4mL of 2N hydrochloric acid was added, it was filtered under suction, dried and recrystallized from 10ml anhydrous ethanol to give 3.6g of N, N-diisopropyl-3-(2-hydroxy-5-methylphenyl)-3-phenylpropylamine, yield was 75%, mp209~211°C. ¹H-NMR (ppm, CDCl₃): 1.20 (m, 12H), 2.15 (s, 3H), 2.70 (m, 2H), 2.90 (m, 2H), 3.51 (t, 2H), 4.50 (t, 1H), 7.25 (m, 8H).